Complete Summary

GUIDELINE TITLE

Diseases characterized by vaginal discharge. Sexually transmitted diseases treatment guidelines 2006.

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention, Workowski KA, Berman SM. Diseases characterized by vaginal discharge. Sexually transmitted diseases treatment guidelines 2006. MMWR Morb Mortal Wkly Rep 2006 Aug 4;55(RR-11):49-56. [222 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Centers for Disease Control and Prevention. Diseases characterized by vaginal discharge. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep 2002 May 10;51(RR-6):42-8.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Bacterial vaginosis
- Trichomoniasis
- Vulvovaginal candidiasis

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Obstetrics and Gynecology
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Managed Care Organizations
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To update the Sexually Transmitted Diseases Treatment Guidelines 2002 (*MMWR 2002;51[No. RR-6]*)
- To assist physicians and other health-care providers in preventing and treating sexually transmitted diseases (STDs)

TARGET POPULATION

Patients with suspected or confirmed bacterial vaginosis, trichomoniasis, and vaginal candidiasis (including pregnant women and women infected with human immunodeficiency virus [HIV]) and their sex partners

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Microscopic examination of fresh vaginal discharge
2. Vaginal pH
3. Gram stain of vaginal discharge
4. Culture for *Candida albicans* and *Trichomonas vaginalis*
5. Evaluation of odor of vaginal discharge after addition of 10% potassium hydroxide (KOH) (whiff test)
6. Evaluation of signs and symptoms
7. DNA probe-based test for high concentrations of *G. vaginalis*

8. Card test for the detection of elevated pH and trimethylamine and prolineaminopeptidase

Treatment/Management

1. Metronidazole (oral or gel)
2. Clindamycin (oral or topical cream, or ovule)
3. Tinidazole (oral)
4. Topical (intravaginal) antifungals such as butoconazole, clotrimazole, miconazole, nystatin, tioconazole, and terconazole
5. Oral fluconazole
6. Follow-up
7. Management of sex partners
8. Special considerations in pregnant and immunocompromised (e.g., HIV-infected) women and in women with allergies or intolerance to antifungal treatment
9. Metronidazole desensitization

MAJOR OUTCOMES CONSIDERED

- Microbiologic cure
- Alleviation of signs and symptoms
- Prevention of sequelae
- Prevention of transmission

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Subjective Review

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Beginning in 2004, the Centers for Disease Control and Prevention (CDC) personnel and professionals knowledgeable in the field of sexually transmitted diseases (STDs) systematically reviewed evidence (including published abstracts and peer-reviewed journal articles) concerning each of the major STDs, focusing on information that had become available since publication of the *Sexually Transmitted Diseases Treatment Guidelines, 2002*. Background papers were written and tables of evidence constructed summarizing the type of study (e.g., randomized controlled trial or case series), study population and setting, treatments or other interventions, outcome measures assessed, reported findings, and weaknesses and biases in study design and analysis. A draft document was developed on the basis of the reviews.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In April 2005, the Centers for Disease Control and Prevention (CDC) staff members and invited consultants assembled in Atlanta, Georgia, for a 3-day meeting to present the key questions regarding sexually transmitted disease (STD) treatment that emerged from the evidence-based reviews and the information available to answer those questions. When relevant, the questions focused on four principal outcomes of STD therapy for each individual disease: 1) microbiologic cure, 2) alleviation of signs and symptoms, 3) prevention of sequelae, and 4) prevention of transmission. Cost-effectiveness and other advantages (e.g., single-dose formulations and directly observed therapy of specific regimens) also were discussed. The consultants then assessed whether the questions identified were relevant, ranked them in order of priority, and attempted to arrive at answers using the available evidence. In addition, the consultants evaluated the quality of evidence supporting the answers on the basis of the number, type, and quality of the studies.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC) and the Centers for Disease Control and Prevention (CDC): When more than one therapeutic regimen is recommended, the sequence is alphabetized unless the choices for therapy are prioritized based on efficacy, convenience, or cost. For sexually transmitted diseases (STDs) with more than one recommended regimen, almost all regimens have similar efficacy and similar rates of intolerance or toxicity unless otherwise specified.

Management of Patients Who Have Vaginal Infections

Vaginitis is usually characterized by a vaginal discharge and/or vulvar itching and irritation, and a vaginal odor might be present. The three diseases most frequently associated with vaginal discharge are bacterial vaginosis (BV) (replacement of the normal vaginal flora by an overgrowth of anaerobic microorganisms, mycoplasmas, and *Gardnerella vaginalis*), trichomoniasis (*Trichomonas vaginalis*), and candidiasis (usually caused by *Candida albicans*). Cervicitis can sometimes cause a vaginal discharge. Although vulvovaginal candidiasis (VVC) usually is not transmitted sexually, it is included in this section because it is frequently diagnosed in women being evaluated for STDs.

Various diagnostic methods are available to identify the etiology of an abnormal vaginal discharge. Laboratory testing fails to identify the cause of vaginitis in a minority of women. The cause of vaginal symptoms usually can be determined by pH and microscopic examination of fresh samples of the discharge. The pH of the vaginal secretions can be determined by narrow-range pH paper; an elevated pH (i.e., >4.5) is common with BV or trichomoniasis but might not be highly specific. Discharge can be further examined by diluting one sample in one to two drops of 0.9% normal saline solution on one slide and a second sample in 10% potassium hydroxide (KOH) solution. An amine odor detected immediately after applying KOH suggests BV. Cover slips are placed on the slides, and they are examined under a microscope at low- and high-dry power. Motile *T. vaginalis* or clue cells (epithelial cells with borders obscured by small bacteria), which are characteristic of BV, usually are identified easily in the saline specimen. White blood counts (WBCs) without evidence of trichomonads or yeast are usually suggestive of cervicitis (see the NGC summary of the CDC guideline Diseases Characterized by Urethritis and Cervicitis, specifically the section on cervicitis). The yeast or pseudohyphae of *Candida* species are more easily identified in the KOH specimen. However, the absence of trichomonads or pseudohyphae does not rule out these infections because several studies have demonstrated the presence of these pathogens by culture or polymerase chain reaction (PCR) after a negative microscopic examination. The presence of objective signs of vulvar inflammation in the absence of vaginal pathogens, along with a minimal amount of discharge, suggests the possibility of mechanical, chemical, allergic, or other noninfectious

irritation of the vulva. Culture for *T. vaginalis* is more sensitive than microscopic examination. In settings where microscopy is not available, alternative point-of-care tests may be used to diagnose vaginitis.

Bacterial Vaginosis

BV is a polymicrobial clinical syndrome resulting from replacement of the normal hydrogen peroxide (H_2O_2-producing *Lactobacillus* species (sp.) in the vagina with high concentrations of anaerobic bacteria (e.g., *Prevotella* sp. and *Mobiluncus* sp.), *G. vaginalis*, and *Mycoplasma hominis*. BV is the most prevalent cause of vaginal discharge or malodor; however, more than 50% of women with BV are asymptomatic. The cause of the microbial alteration is not fully understood. BV is associated with having multiple sex partners, a new sex partner, douching, and lack of vaginal lactobacilli; whether BV results from acquisition of a sexually transmitted pathogen is unclear. Women who have never been sexually active are rarely affected. Treatment of male sex partners has not been beneficial in preventing the recurrence of BV.

Diagnostic Considerations

BV can be diagnosed by the use of clinical criteria or Gram stain. Clinical criteria require three of the following symptoms or signs:

- homogeneous, thin, white discharge that smoothly coats the vaginal walls
- presence of clue cells on microscopic examination
- pH of vaginal fluid >4.5; and
- a fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test)

When a Gram stain is used, determining the relative concentration of lactobacilli (long Gram-positive rods), Gram-negative and Gram-variable rods and cocci (i.e., *G. vaginalis*, *Prevotella*, *Porphyromonas*, and peptostreptococci), and curved Gram-negative rods (*Mobiluncus*) characteristic of BV is considered the gold standard laboratory method for diagnosing BV. Culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific. However, a DNA probe-based test for high concentrations of *G. vaginalis* (Affirm™ VP III, Becton Dickinson, Sparks, Maryland) might have clinical utility. Cervical Papaniculaou (Pap) tests have no clinical utility for the diagnosis of BV because of low sensitivity. Other commercially available tests that might be useful for the diagnosis of BV include a card test for the detection of elevated pH and trimethylamine (QuickVue Advance™, Quidel, San Diego, California) and proline-aminopeptidase (Pip Activity TestCard™, Quidel, San Diego, California).

Treatment

The established benefits of therapy for BV in nonpregnant women are to 1) relieve vaginal symptoms and signs of infection and 2) reduce the risk for infectious complications after abortion or hysterectomy. Other potential benefits might include a reduction in risk for other infections (e.g., HIV and other STDs). All women who have symptomatic disease require treatment.

BV during pregnancy is associated with adverse pregnancy outcomes, including premature rupture of the membranes, preterm labor, preterm birth, intraamniotic infection, and postpartum endometritis. The established benefit of therapy for BV in pregnant women is to relieve vaginal symptoms and signs of infection. Additional potential benefits of therapy include 1) reducing the risk for infectious complications associated with BV during pregnancy and 2) reducing the risk for other infections (e.g., other STDs or HIV). The results of several investigations indicate that treatment of pregnant women with BV who are at high risk for preterm delivery (i.e., those who previously delivered a premature infant) might reduce the risk for prematurity. Therefore, clinicians should consider evaluation and treatment of high-risk pregnant women with asymptomatic BV.

The bacterial flora that characterizes BV have been recovered from the endometria and salpinges of women who have pelvic inflammatory disease (PID). BV has been associated with endometritis, PID, and vaginal cuff cellulitis after invasive procedures, including endometrial biopsy, hysterectomy, hysterosalpingography, placement of an intrauterine device (IUD), cesarean section, and uterine curettage. The results of two randomized controlled trials have indicated that treatment of BV with metronidazole substantially reduced post-abortion PID. Three trials that evaluated the use of anaerobic antimicrobial coverage (i.e., metronidazole) for routine operative prophylaxis before abortion and seven trials that evaluated this additional coverage for women undergoing hysterectomy demonstrated a substantial reduction in postoperative infectious complications. Because of the increased risk for postoperative infectious complications associated with BV, some specialists recommend that before performing surgical abortion or hysterectomy, providers should screen and treat women with BV in addition to providing routine prophylaxis. However, more information is needed before recommending treatment of asymptomatic BV before other invasive procedures.

Recommended Regimens

- **Metronidazole** 500 mg orally twice a day for 7 days

  OR

- **Metronidazole gel**, 0.75%, one full applicator (5g) intravaginally, once a day for 5 days

  OR

- **Clindamycin cream**, 2%, one full applicator (5g) intravaginally at bedtime for 7 days

Patients should be advised to avoid consuming alcohol during treatment with metronidazole and for 24 hours thereafter. Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for 5 days after use. Refer to clindamycin product labeling for additional information. Topical clindamycin preparations should not be used in the second half of pregnancy.

The recommended metronidazole regimens are equally efficacious. The recommended intravaginal clindamycin regimen might be less efficacious than the metronidazole regimens. One randomized trial evaluated the clinical equivalency of intravaginal metronidazole gel 0.75% once daily versus twice daily and demonstrated similar cure rates 1 month after therapy.

Alternative Regimens

- Clindamycin 300 mg orally twice a day for 7 days

  OR

- Clindamycin ovules 100 g intravaginally once at bedtime for 3 days

Metronidazole 2 g single-dose therapy has the lowest efficacy for BV and is no longer a recommended or alternative regimen. The Food and Drug Administration (FDA) has cleared metronidazole 750 mg extended release tablets once daily for 7 days and a single dose of clindamycin intravaginal cream. No data have been published that compares the clinical or microbiologic equivalencies of these regimens with other regimens. Cure rates do not differ between intravaginal clindamycin cream and ovules.

Several studies have evaluated the clinical and microbiologic efficacy of using lactobacillus intravaginal suppositories to restore normal flora and treat BV. However, no currently available lactobacillus suppository was determined to be better than placebo 1 month after therapy for either clinical or microbiologic cure. No data support the use of douching for treatment or relief of symptoms.

Follow-Up

Follow-up visits are unnecessary if symptoms resolve. Because recurrence of BV is not unusual, women should be advised to return for additional therapy if symptoms recur. A treatment regimen different from the original regimen may be used to treat recurrent disease. However, women with multiple recurrences should be managed in consultation with a specialist. One randomized trial for persistent BV indicated that metronidazole gel 0.75% twice per week for 6 months after completion of a recommended regimen was effective in maintaining a clinical cure for 6 months.

Management of Sex Partners

The results of clinical trials indicate that a woman's response to therapy and the likelihood of relapse or recurrence are not affected by treatment of her sex partner(s). Therefore, routine treatment of sex partners is not recommended.

Special Considerations

Allergy or Intolerance to the Recommended Therapy

Intravaginal clindamycin cream is preferred in case of allergy or intolerance to metronidazole. Intravaginal metronidazole gel can be considered for patients who do not tolerate systemic metronidazole, but patients allergic to oral metronidazole should not be administered intravaginal metronidazole.

Pregnancy

All pregnant women who have symptomatic disease require treatment. BV has been associated with adverse pregnancy outcomes (e.g., premature rupture of the membranes, chorioamnionitis, preterm labor, preterm birth, intraamniotic infection, postpartum endometritis, and postcesarean wound infection). Some specialists prefer using systemic therapy to treat possible subclinical upper genital tract infections.

Treatment of BV in asymptomatic pregnant women at high risk for preterm delivery (i.e., those who have previously delivered a premature infant) with a recommended oral regimen has reduced preterm delivery in three of four randomized controlled trials; some specialists recommend screening and oral treatment of these women. However, the optimal treatment regimens have not been established. Screening (if conducted) and treatment should be performed during the first prenatal visit.

Two trials that evaluated the efficacy of metronidazole during pregnancy used the 250-mg regimen. However, some specialists suggest using a regimen of 500 mg twice daily in pregnant women. One small trial demonstrated that treatment with oral metronidazole 500 mg twice daily was equally effective as metronidazole gel, with cure rates of 70%. These regimens were not effective in reducing preterm birth in any group of women. Multiple studies and meta-analyses have not demonstrated an association between metronidazole use during pregnancy and teratogenic or mutagenic effects in newborns.

Recommended Regimens for Pregnant Women

- **Metronidazole** 500 mg orally twice a day for 7 days

  OR

- **Metronidazole** 250 mg orally three times a day for 7 days

  OR

- **Clindamycin** 300 mg orally twice a day for 7 days

Whether treatment of asymptomatic pregnant women with BV who are at low risk for preterm delivery reduces adverse outcomes of pregnancy is unclear. One trial in which oral clindamycin was used demonstrated a reduction in spontaneous preterm birth. Several trials have evaluated the use of intravaginal clindamycin during pregnancy to reduce preterm birth and treat asymptomatic BV. One trial in which women were treated before 20 weeks' gestation demonstrated a reduction in preterm birth. In three other trials, intravaginal clindamycin cream was administered at 16-32 weeks' gestation, and an increase in adverse events (e.g.,

low birthweight and neonatal infections) was observed in newborns. Therefore, intravaginal clindamycin cream should only be used during the first half of pregnancy.

Follow-Up of Pregnant Women

Treatment of BV in asymptomatic pregnant women who are at high risk for preterm delivery might prevent adverse pregnancy outcomes. Therefore, a follow-up evaluation 1 month after completion of treatment should be considered to evaluate whether therapy was effective.

HIV Infection

Patients who have BV and also are infected with HIV should receive the same treatment regimen as those who are HIV negative. BV appears to be more persistent in HIV-positive women.

Trichomoniasis

Trichomoniasis is caused by the protozoan *T. vaginalis*. Some men who are infected with *T. vaginalis* might not have symptoms; others have nongonococcal urethritis (NGU). Many infected women have symptoms characterized by a diffuse, malodorous, yellow-green vaginal discharge with vulvar irritation. However, some women have minimal or no symptoms.

Diagnosis of vaginal trichomoniasis is usually performed by microscopy of vaginal secretions, but this method has a sensitivity of only approximately 60%-70% and requires immediate evaluation of wet preparation slide for optimal results. Other FDA-cleared tests for trichomoniasis in women include OSOM® Trichomonas Rapid Test (Genzyme Diagnostics, Cambridge, Massachusetts), an immunochromatographic capillary flow dipstick technology, and the Affirm™ VP III (Becton Dickenson, San Jose, California), a nucleic acid probe test that evaluates for *T. vaginalis*, *G. vaginalis*, and *C. albicans*. These tests are both performed on vaginal secretions and have a sensitivity >83% and a specificity >97%. Both tests are point-of-care diagnostics. The results of the OSOM® Trichomonas Rapid Test are available in approximately 10 minutes, and results of the Affirm™ VP III are available within 45 minutes. Although these tests tend to be more sensitive than vaginal wet preparation, false positives might occur especially in low prevalence populations. Culture is the most sensitive and specific commercially available method of diagnosis. In women in whom trichomoniasis is suspected but not confirmed by microscopy, vaginal secretions should be cultured for *T. vaginalis*.

In men, wet preparation is insensitive, and culture testing of urethral swab, urine, and semen is required for optimal sensitivity. No FDA-cleared PCR test for *T. vaginalis* is available in the United States, but such testing might be available from commercial laboratories that have developed their own PCR tests.

Recommended Regimens

- **Metronidazole** 2 g orally in a single dose

OR

- **Tinidazole** 2 g orally in a single dose

Alternative Regimen

- **Metronidazole** 500 mg orally twice a day for 7 days

Patients should be advised to avoid consuming alcohol during treatment with metronidazole or tinidazole. Abstinence from alcohol use should continue for 24 hours after completion of metronidazole or 72 hours after completion of tinidazole.

The nitroimidazoles comprise the only class of drugs useful for the oral or parenteral therapy of trichomoniasis. Of these drugs, metronidazole and tinidazole are available in the United States and are cleared by the FDA for the treatment of trichomoniasis. In randomized clinical trials, the recommended metronidazole regimens have resulted in cure rates of approximately 90%-95%, and the recommended tinidazole regimen has resulted in cure rates of approximately 86%-100%. The appropriate treatment of sex partners might increase these reported rates. Randomized controlled trials comparing single 2 g doses of metronidazole and tinidazole suggest that tinidazole is equivalent to, or superior to, metronidazole in achieving parasitologic cure and resolution of symptoms. Treatment of patients and sex partners results in relief of symptoms, microbiologic cure, and reduction of transmission.

Metronidazole gel is considerably less efficacious for the treatment of trichomoniasis (<50%) than oral preparations of metronidazole. Topically applied antimicrobials (e.g., metronidazole gel) are unlikely to achieve therapeutic levels in the urethra or perivaginal glands; therefore, use of the gel is not recommended. Several other topically applied antimicrobials occasionally have been used for treatment of trichomoniasis; however, these preparations probably do not have greater efficacy than metronidazole gel.

Follow-Up

Follow-up is unnecessary for men and women who become asymptomatic after treatment or who are initially asymptomatic. Some strains of *T. vaginalis* can have diminished susceptibility to metronidazole; however, infections caused by the majority of these organisms respond to tinidazole or higher doses of metronidazole. Low-level metronidazole resistance has been identified in 2%-5% of cases of vaginal trichomoniasis. High-level resistance is rare. Tinidazole has a longer serum half-life and reaches higher levels in genitourinary tissues than metronidazole. In addition, many *T. vaginalis* isolates have lower minimum inhibitory concentrations (MICs) to tinidazole than metronidazole.

If treatment failure occurs with metronidazole 2 g single dose and reinfection is excluded, the patient can be treated with metronidazole 500 mg orally twice daily for 7 days or tinidazole 2 g single dose. For patients failing either of these regimens, clinicians should consider treatment with tinidazole or metronidazole at 2 g orally for 5 days. If these therapies are not effective, further management

should be discussed with a specialist. The consultation should ideally include determination of the susceptibility of *T. vaginalis* to metronidazole and tinidazole. Consultation and *T. vaginalis* susceptibility testing is available from CDC (telephone: 770-488-4115; website: http://www.cdc.gov/std).

Management of Sex Partners

Sex partners of patients with *T. vaginalis* should be treated. Patients should be instructed to avoid sex until they and their sex partners are cured (i.e., when therapy has been completed and patient and partner(s) are asymptomatic).

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Metronidazole and tinidazole are both nitroimidazoles. Patients with an immediate-type allergy to a nitroimidazole can be managed by metronidazole desensitization in consultation with a specialist. Topical therapy with drugs other than nitroimidazoles can be attempted, but cure rates are low (<50%).

Pregnancy

Vaginal trichomoniasis has been associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and low birthweight. However, data do not suggest that metronidazole treatment results in a reduction in perinatal morbidity. Although some trials suggest the possibility of increased prematurity or low birthweight after metronidazole treatment, limitations of the studies prevent definitive conclusions regarding risks of treatment. Treatment of *T. vaginalis* might relieve symptoms of vaginal discharge in pregnant women and might prevent respiratory or genital infection of the newborn and further sexual transmission. Clinicians should counsel patients regarding the potential risks and benefits of treatment. Some specialists would defer therapy in asymptomatic pregnant women until after 37 weeks' gestation. In addition, these pregnant women should be provided careful counseling regarding condom use and the continued risk of sexual transmission.

Women may be treated with 2 g of metronidazole in a single dose. Metronidazole is pregnancy category B (animal studies have revealed no evidence of harm to the fetus, but no adequate, well-controlled studies among pregnant women have been conducted). Multiple studies and meta-analyses have not demonstrated a consistent association between metronidazole use during pregnancy and teratogenic or mutagenic effects in infants. Tinidazole is pregnancy category C (animal studies have demonstrated an adverse event, and no adequate, well-controlled studies in pregnant women have been conducted), and its safety in pregnant women has not been well-evaluated.

In lactating women who are administered metronidazole, withholding breastfeeding during treatment and for 12-24 hours after the last dose will reduce the exposure of metronidazole to the infant. While using tinidazole, interruption of breastfeeding is recommended during treatment and for 3 days after the last dose.

HIV Infection

Patients who have trichomoniasis and also are infected with HIV should receive the same treatment regimen as those who are HIV negative. The incidence, persistence, and recurrence of trichomoniasis in HIV-infected women are not correlated with immune status.

Vulvovaginal Candidiasis

VVC usually is caused by *C. albicans* but occasionally is caused by other *Candida* sp. or yeasts. Typical symptoms of VVC include pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge. None of these symptoms is specific for VVC. An estimated 75% of women will have at least one episode of VVC, and 40%-45% will have two or more episodes. On the basis of clinical presentation, microbiology, host factors, and response to therapy, VVC can be classified as either uncomplicated or complicated. Approximately 10%-20% of women will have complicated VVC, suggesting diagnostic and therapeutic considerations.

Classification of Vulvovaginal Candidiasis (VVC)

Uncomplicated VVC	Complicated VVC
• Sporadic or infrequent VVC	• Recurrent VVC
AND	**OR**
• Mild-to-moderate VVC	• Severe VVC
AND	**OR**
• Likely to be *Candida albicans*	• Nonalbicans candidiasis
AND	**OR**
• Nonimmunocompromised women	• Women with uncontrolled diabetes, debilitation, or immunosuppression, or those who are pregnant

Uncomplicated VVC

Diagnostic Considerations in Uncomplicated VVC

A diagnosis of *Candida* vaginitis is suggested clinically by the presence of external dysuria and vulvar pruritus, pain, swelling, and redness. Signs include vulvar edema, fissures, excoriations, or thick curdy vaginal discharge. The diagnosis can be made in a woman who has signs and symptoms of vaginitis when either 1) a wet preparation (saline, 10% KOH) or Gram stain of vaginal discharge demonstrates yeasts or pseudohyphae or 2) a culture or other test yields a positive result for a yeast species. *Candida* vaginitis is associated with a normal vaginal pH (<4.5). Use of 10% KOH in wet preparations improves the visualization of yeast and mycelia by disrupting cellular material that might obscure the yeast or pseudohyphae. Examination of a wet mount with KOH preparation should be performed for all women with symptoms or signs of VVC,

and women with a positive result should receive treatment. For those with negative wet mounts, vaginal cultures for *Candida* should be considered for those with any sign or multiple symptoms. If *Candida* cultures cannot be done, empiric treatment can be considered for symptomatic women with any sign of VVC on examination when the wet mount is negative. Identifying *Candida* by culture in the absence of symptoms or signs is not an indication for treatment because approximately 10%-20% of women harbor *Candida* sp. and other yeasts in the vagina. VVC can occur concomitantly with STDs. The majority of healthy women with uncomplicated VVC have no identifiable precipitating factors.

Treatment

Short-course topical formulations (i.e., single dose and regimens of 1-3 days) effectively treat uncomplicated VVC. The topically applied azole drugs are more effective than nystatin. Treatment with azoles results in relief of symptoms and negative cultures in 80%-90% of patients who complete therapy.

Recommended Regimens

Intravaginal Agents:

- **Butoconazole** 2% cream 5 g intravaginally for 3 days*

  OR

- **Butoconazole** 2% cream 5 g (Butaconazole1-sustained release), single intravaginal application

  OR

- **Clotrimazole** 1% cream 5 g intravaginally for 7--14 days*

  OR

- **Clotrimazole** 100 mg vaginal tablet for 7 days

  OR

- **Clotrimazole** 100 mg vaginal tablet, two tablets for 3 days

  OR

- **Miconazole** 2% cream 5 g intravaginally for 7 days*

  OR

- **Miconazole** 100 mg vaginal suppository, one suppository for 7 days*

  OR

- **Miconazole** 200 mg vaginal suppository, one suppository for 3 days*

  OR

- **Miconazole** 1,200 mg vaginal suppository, one suppository for 1 day*

  OR

- **Nystatin** 100,000-unit vaginal tablet, one tablet for 14 days

  OR

- **Tioconazole** 6.5% ointment 5 g intravaginally in a single application*

  OR

- **Terconazole** 0.4% cream 5 g intravaginally for 7 days

  OR

- **Terconazole** 0.8% cream 5 g intravaginally for 3 days

  OR

- **Terconazole** 80 mg vaginal suppository, one suppository for 3 days

Oral Agent:

- **Fluconazole** 150 mg oral tablet, one tablet in single dose

* Over-the-counter preparations.

The creams and suppositories in this regimen are oil-based and might weaken latex condoms and diaphragms. Refer to condom product labeling for further information.

Intravaginal preparations of butoconazole, clotrimazole, miconazole, and tioconazole are available over-the-counter (OTC). Women whose condition has previously been diagnosed with VVC are not necessarily more likely to be able to diagnose themselves; therefore, any woman whose symptoms persist after using an OTC preparation, or who has a recurrence of symptoms within 2 months, should be evaluated with office-based testing. Unnecessary or inappropriate use of OTC preparations is common and can lead to a delay in the treatment of other vulvovaginitis etiologies, which can result in adverse clinical outcomes.

Follow-Up

Patients should be instructed to return for follow-up visits only if symptoms persist or recur within 2 months of onset of initial symptoms.

Management of Sex Partners

VVC is not usually acquired through sexual intercourse; treatment of sex partners is not recommended but may be considered in women who have recurrent infection. A minority of male sex partners might have balanitis, which is characterized by erythematous areas on the glans of the penis in conjunction with pruritus or irritation. These men benefit from treatment with topical antifungal agents to relieve symptoms.

Special Considerations

Allergy, Intolerance, and Adverse Reactions. Topical agents usually cause no systemic side effects, although local burning or irritation might occur. Oral agents occasionally cause nausea, abdominal pain, and headache. Therapy with the oral azoles has been associated rarely with abnormal elevations of liver enzymes. Clinically important interactions can occur when these oral agents are administered with other drugs, including astemizole, calcium channel antagonists, cisapride, coumadin, cyclosporin A, oral hypoglycemic agents, phenytoin, protease inhibitors, tacrolimus, terfenadine, theophylline, trimetrexate, and rifampin.

Complicated VVC

Recurrent Vulvovaginal Candidiasis (RVVC)

RVVC, usually defined as four or more episodes of symptomatic VVC in 1 year, affects a small percentage of women (<5%). The pathogenesis of RVVC is poorly understood, and the majority of women with RVVC have no apparent predisposing or underlying conditions. Vaginal cultures should be obtained from patients with RVVC to confirm the clinical diagnosis and to identify unusual species, including nonalbicans species, particularly *Candida glabrata* (*C. glabrata* does not form pseudohyphae or hyphae and is not easily recognized on microscopy). *C. glabrata* and other nonalbicans *Candidia* species are observed in 10%-20% of patients with RVVC. Conventional antimycotic therapies are not as effective against these species as against *C. albicans*.

Treatment

Each individual episode of RVVC caused by *C. albicans* responds well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., 7-14 days of topical therapy or a 100 mg, 150 mg, or 200 mg oral dose of fluconazole every third day for a total of 3 doses (day 1, 4, and 7) to attempt mycologic remission before initiating a maintenance antifungal regimen.

Maintenance Regimens

Oral fluconazole (i.e., 100-mg, 150-mg, or 200-mg dose) weekly for 6 months is the first line of treatment. If this regimen is not feasible, some specialists

recommend topical clotrimazole 200 mg twice a week, clotrimazole (500-mg dose vaginal suppositories once weekly), or other topical treatments used intermittently.

Suppressive maintenance antifungal therapies are effective in reducing RVVC. However, 30%-50% of women will have recurrent disease after maintenance therapy is discontinued. Routine treatment of sex partners is controversial. *C. albicans* azole resistance is rare in vaginal isolates, and susceptibility testing is usually not warranted for individual treatment guidance.

Severe VVC

Severe vulvovaginitis (i.e., extensive vulvar erythema, edema, excoriation, and fissure formation) is associated with lower clinical response rates in patients treated with short courses of topical or oral therapy. Either 7-14 days of topical azole or 150 mg of fluconazole in two sequential doses (second dose 72 hours after initial dose) is recommended.

Nonalbicans VVC

The optimal treatment of nonalbicans VVC remains unknown. Options include longer duration of therapy (7-14 days) with a nonfluconazole azole drug (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for 2 weeks. This regimen has clinical and mycologic eradication rates of approximately 70%. If symptoms recur, referral to a specialist is advised.

Compromised Host

Women with underlying debilitating medical conditions (e.g., those with uncontrolled diabetes or those receiving corticosteroid treatment) do not respond as well to short-term therapies. Efforts to correct modifiable conditions should be made, and more prolonged (i.e., 7-14 days) conventional antimycotic treatment is necessary.

Pregnancy

VVC frequently occurs during pregnancy. Only topical azole therapies, applied for 7 days, are recommended for use among pregnant women.

HIV Infection

The incidence of VVC in HIV-infected women is unknown. Vaginal *Candida* colonization rates among HIV-infected women are higher than among those for seronegative women with similar demographic characteristics and high-risk behaviors, and the colonization rates correlate with increasing severity of immunosuppression. Symptomatic VVC is more frequent in seropositive women and similarly correlates with severity of immunodeficiency. In addition, among HIV-infected women, systemic azole exposure is associated with the isolation of nonalbicans *Candida* species from the vagina.

Based on available data, therapy for VVC in HIV-infected women should not differ from that for seronegative women. Although long-term prophylactic therapy with fluconazole at a dose of 200 mg weekly has been effective in reducing *C. albicans* colonization and symptomatic VVC, this regimen is not recommended for routine primary prophylaxis in HIV-infected women in the absence of recurrent VVC. Given the frequency at which RVVC occurs in the immunocompetent healthy population, the occurrence of RVVC should not be considered an indication for HIV testing.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

Throughout the 2006 guideline document, the evidence used as the basis for specific recommendations is discussed briefly. More comprehensive, annotated discussions of such evidence will appear in background papers that will be published in a supplement issue of the journal *Clinical Infectious Diseases*.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis and management of bacterial vaginosis, trichomoniasis, and vaginal candidiasis

POTENTIAL HARMS

- Topical agents usually cause no systemic side effects, although local burning may occur. Oral agents occasionally cause nausea, abdominal pain, and headache. Therapy with the oral azoles has been associated rarely with abnormal elevations of liver enzymes. Hepatotoxicity secondary to ketoconazole therapy occurs in an estimated one of every 10,000-15,000 exposed persons. Clinically important interactions might occur when oral agents are administered with other drugs including astemizole, calcium channel antagonists, cisapride, coumadin, cyclosporin A, oral hypoglycemic agents, phenytoin, protease inhibitors, tacrolimus, terfenadine, theophylline, trimetrexate, and rifampin.
- Butoconazole, clotrimazole, miconazole, tioconazole, and terconazole creams and suppositories are oil-based and might weaken latex condoms and diaphragms; refer to condom product labeling for additional information
- Clindamycin cream and ovules are oil-based and might weaken latex condoms and diaphragms; refer to condom product labeling for additional information.

- The use of clindamycin cream during the second half of pregnancy is not recommended because evidence from several trials suggests an increase in adverse events (e.g., low birth weight and neonatal infection).
- Tinidazole is pregnancy category C (animal studies have demonstrated an adverse event, and no adequate, well-controlled studies in pregnant women have been conducted), and its safety in pregnant women has not been well-evaluated.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These recommendations were developed in consultation with public- and private-sector professionals knowledgeable in the treatment of patients with sexually transmitted diseases (STDs). The recommendations are applicable to various patient-care settings, including family planning clinics, private physicians' offices, managed care organizations, and other primary-care facilities.
- These recommendations are meant to serve as a source of clinical guidance: health-care providers should always consider the individual clinical circumstances of each person in the context of local disease prevalence. These guidelines focus on the treatment and counseling of individual patients and do not address other community services and interventions that are important in sexually transmitted disease STD/human immunodeficiency virus (HIV) prevention.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention, Workowski KA, Berman SM. Diseases characterized by vaginal discharge. Sexually transmitted diseases treatment guidelines 2006. MMWR Morb Mortal Wkly Rep 2006 Aug 4;55(RR-11):49-56. [222 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1993 (revised 2006 Aug 4)

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]

GUIDELINE DEVELOPER COMMENT

These guidelines for the treatment of persons who have sexually transmitted diseases (STDs) were developed by CDC after consultation with a group of professionals knowledgeable in the field of STDs who met in Atlanta, Georgia, during April 19–21, 2005.

SOURCE(S) OF FUNDING

United States Government

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Not stated

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Centers for Disease Control and Prevention. Diseases characterized by vaginal discharge. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep 2002 May 10;51(RR-6):42-8.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Centers for Disease Control and Prevention (CDC) Web site:

- HTML Format
- Portable Document Format (PDF)

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Workowski KA, Levine WC, Wasserheit JN. U.S. Centers for Disease Control and Prevention guidelines for the treatment of sexually transmitted diseases: an opportunity to unify clinical and public health practice. Ann Intern Med. 2002 Aug 20;137(4):255-62. Electronic copies: Available through Annals of Internal Medicine Online.
- The CDC Sexually Transmitted Diseases Treatment Guidelines 2004 for PDA or Palm OS. Available from the CDC National Prevention Information Network (NPIN) Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 2002. This summary was updated by ECRI on October 11, 2006.

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